UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

HED DOC. NO. 014313

DATE: **August 30, 2000**

MEMORANDUM

SUBJECT: ***ACEPHATE:*** Support for the Toxicology Endpoint Selection - for Dermal and Inhalation Risk Assessments; Report of the Hazard Identification Assessment Review Committee

FROM: Nancy McCarroll
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THROUGH: Jess Rowland, Co-Chair
and
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TO: Felicia Fort, Risk Assessor
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and

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PC Code: 103301

On July 19, 2000, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for

Acephate with regard to the dermal and inhalation toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. This memorandum records the decisions of the HIARC regarding the submission of new Acephate data by the Registrant on June 2, 2000. These data include a new 21-day dermal toxicity study in rats (MRID No. 45134301) and a 4-week "nose only" inhalation toxicity study in rats (MRID No. 45134302) which were considered in the Revised Short-, Intermediate-, and Long Term Dermal Risk Assessment as well as the Revised Inhalation (any duration) Risk Assessments. The potential for increased susceptibility of infants and children from exposure to Acephate was previously evaluated as required by the Food Quality Protection Act (FQPA) of 1996.

Committee Members in Attendance

Members present were: William Burnam, Jess Rowland, Elizabeth Doyle, Brenda Tarplee, Elizabeth Mendez, David Nixon, Yung Yang, Jonathan Chen, and Ayaad Assaad

Member(s) in absentia: Pamela Hurley

Data evaluation prepared by: Nancy McCarroll, Toxicology Branch 1

Also in attendance were: Catherine Joseph, RRB1, Monica Alvarez, SRRD

Data Evaluation / Report Presentation: July 19, 2000

Nancy McCarroll
Toxicologist

1. BACKGROUND

Toxicology Endpoint Selection for Dermal Risk Assessments

On July 20, 1999, a memorandum was issued documenting the conclusions of the EPA reviewers and the expert toxicologist member of the HIARC. It was concluded that the decisions of the Committee meeting held on December 11, 1997, regarding the Short- and Intermediate-Term dermal risk assessment for Acephate, were valid and should remain unchanged (see HED Document No. 013613). Accordingly, a NOAEL of 12 mg/kg/day was selected for Acephate from the 21-day dermal toxicity study in rats and was based on brain cholinesterase inhibition at the next higher dose (60 mg/kg/day), which was selected as the systemic LOAEL (see HED document No. 012453). These deliberations were undertaken in response to the Registrant's request that the Agency consider both the 21-day study and the 5-day pilot study for the dermal scenarios (see HED Document No. 013396). Based on this reconsideration of the data, EPA reviewers and the expert dermal toxicologist member of the HIARC, Dr. P.V. Shah concluded that the effects at 60 mg/kg/day were valid in the main 21-day dermal study because cholinesterase inhibition occurred in a dose-related manner, was statistically significant and was seen in the most sensitive parameter (brain). The systemic LOAEL was, therefore, set at 60 mg/kg/day; the NOAEL was 12 mg/kg/day.

On June 2, 2000, the Registrant submitted a new 21-day dermal toxicity in rats (MRID No. 45134301) for review and for consideration in the re-evaluation of the dermal NOAEL and LOAEL for the dermal risk assessments.

Toxicology Endpoint Selection for Inhalation Risk Assessments

On July 20, 1999, the Agency responded to the Registrant's comment regarding the use of "whole body" subchronic inhalation studies to set the NOAEL for the inhalation risk assessments because the "NOEL for the two subchronic inhalation studies with Acephate is an underestimate of the actual NOEL" (see HED Document No. 013416). At that time, the Agency agreed with the Registrant that the total exposure in a whole-body exposure chamber is greater than a "nose only" exposure. However, the Agency noted that it has no policy on this issue and that adjustment corrections for the oral and dermal exposure routes are not performed. Consequently, the NOAEL, based on brain cholinesterase inhibition, remained unchanged at 0.0005 mg/L (see HED Document No. 012453 for report of the Hazard Identification Committee meeting held on December 11, 1997 and HED Document No. 012544 for Executive Summary on the whole body subchronic inhalation study, MRID No. 40645903).

On June 2, 2000, the Registrant submitted a new 4-week inhalation study (nose only) in rats (MRID No. 45134302) for review and for consideration in the re-evaluation of the inhalation NOAEL and LOAEL for the inhalation risk assessments.

2. HAZARD IDENTIFICATION

Occupational/Residential Exposure

2.1 Short-Term Dermal (1 - 7 days) Exposure

Selected Study: Repeated Dose (21-Day) Dermal Toxicity in Rats

Guideline #: [82-2] Study OPPTS 870.3200

MRID No.: 45134301

Executive Summary: In a repeated dose dermal toxicity study (MRID 45134301), acephate (tech., 98.8% a.i.) was applied to the shaved dorsal skin of 10 Crl:CD®(SD)IGS BR rats/sex/dose in 0.9% saline vehicle (1 ml/kg body weight) at concentrations of 0, 20, 30, 40 or 50 mg/kg/day, 5 days/week, 6 hrs/day over 21 days (total of 16 applications).

No treatment-related mortality or clinical signs (including local dermal irritation at the application site) and no effects on body weights, food consumption, cholinesterase activities (plasma, RBC or brain) or gross observations at necropsy were reported. Hematology, clinical chemistry, urinalysis, organ weight determinations and microscopic examination of tissues were not performed. **The systemic toxicity (ChE) LOAEL is >50 mg/kg/day (HDT) and the NOAEL is 50 mg/kg/day. The LOAEL for local dermal irritation is >50 mg/kg/day and the NOAEL is 50 mg/kg/day.**

This 21-day dermal toxicity study is classified **Acceptable/nonguideline**.

Proposed Dose and Endpoint: 50 mg/kg/day; NOAEL for systemic toxicity (i.e., ChE inhibition)

Comments about Study/Endpoint: By itself, the selected study does not satisfy the guideline requirement for a 21-day dermal toxicity study (§82-2). This is because of the lack of evaluation of hematology and clinical chemistry other than ChE, organ weights and microscopic pathology. The study is, nevertheless, acceptable when considered together with an earlier 21-day dermal toxicity in the rat (MRID 44541101; see review in HED Doc. No. 013396). Based on the reconsideration of all of the data including the recently submitted findings, the HIARC concluded that the LOAEL of 60 mg/kg/day from the earlier study (MRID No. 44541101) should be maintained and a NOAEL of 50 mg/kg/day from the new study (MRID No. 45134301) should be selected. The NOAEL was based on the endpoint of slight but statistically significant inhibition in brain cholinesterase activity in females at the LOAEL of 60 mg/kg/day.

The selected study is considered appropriate for the following reasons : (1) measurements of the most critical parameter (brain and blood inhibition) were taken during the treatment

period, which encompasses the exposure period of concern and (2) the data are in good agreement with the previous study (MRID No. 44541101) showing a NOAEL <60 mg/kg/day and $12 mg/kg/day. In agreement with decisions made at the earlier HAZID meeting, the available acute dermal toxicity study was not used because the dosing regimen did not cover the exposure period of 1-7 days and repeated exposures were not evaluated.

2.2 Intermediate-term Dermal (1-Week to Several Months) Exposure

Selected Study: 21-Day Dermal Toxicity in Rats Guideline #: [82-2] OPPTS 870.3200

MRID No.: 45134301

Executive Summary: See SHORT-TERM DERMAL

Proposed Dose and Endpoint: 50 mg/kg/day; NOAEL for systemic toxicity (i.e., ChE inhibition). The HIARC detemined that the 21-day dermal toxicity study was appropriate for this exposure scenario since ChE inhibition was not progressive with time.

Comments about Study/Endpoint: See SHORT-TERM DERMAL for comments.

2.3 Long-term Dermal (Several Months to Lifetime)

Selected Study: 21-Day Dermal Toxicity in Rats Guideline #: [82-2] Study in OPPTS 870.3200

MRID No.: 45134301

Executive Summary: See SHORT-TERM DERMAL

Proposed Dose and Endpoint: 50 mg/kg/day; NOAEL for systemic toxicity (i.e., ChE inhibition)

Comments about Study/Endpoint: The subchronic study was used for the risk assessment for long-term duration since ChE inhibition was not progressive with time.

2.4 Inhalation Exposure (All Durations)

Selected Study: 28-Day Subchronic Inhalation Toxicity Study in the Rat Guideline #: [82-4] OPPTS 870.3465

MRID No.: 45134302

Executive Summary: In a subchronic inhalation toxicity study (MRID 45134302) acephate (tech., 98.8% a.i.) aerosol was administered by nose-only inhalation exposure to 10 Crl:CD®(SD)IGS BR rats/sex/concentration at levels of 0.000, 0.001064, 0.003123 or 0.005550 mg/L (target concentrations of 0.000, 0.001, 0.003 or 0.005 mg/L) for 4 weeks (5 days/week and 6 hrs/day; total of 20 exposures).

At 0.003123 mg/L, slightly decreased brain cholinesterase activity in males (-9.9% less than controls, $p<0.01$; females showed a very slight but not significant decrease of -5.2%); plasma cholinesterase in males on days 1 and 5 (-13.5% and -17.1%) and erythrocyte activity in females on day 5 (-21.4%; $p<0.05$) were observed. At 0.005550 mg/L, inhibition of cholinesterase activity in plasma (males -13.5%, $p<0.05$ to -18%, $p<0.01$ on days 1 and 5), erythrocytes (females -30%, day 5) and brain (-14.3%, males and -13.1%, $p<0.01$) was observed along with labored breathing in 25% to 33% of the animals during exposure on 3 days during the last week of the study. (A decrease of -11.6%, $p<0.05$, in plasma cholinesterase activity in males on day 5 at 0.001064 mg/L was considered insufficient for establishing an adverse effect). There were no treatment-related effects on body weight/weight gain, food consumption, organ weights, gross pathology or microscopic findings in the selected tissues that were examined (see DER). Ophthalmological examinations, hematology, clinical chemistry and a complete histopathology Although the study lacks evaluations of several parameters that are normally conducted in a subchronic inhalation study, it is considered acceptable, when taken together with previously conducted 4-week subchronic whole-body exposure inhalation toxicity studies (MRIDs 40504818 and 40645903; HED Doc. No 012433), for determination of ChE and systemic toxicity NOAELs because the most sensitive endpoint, cholinesterase inhibition of blood and brain, was evaluated. examination were not performed. **The ChE LOAEL is 0.003123 mg/L, based on inhibition of plasma and brain cholinesterase activities in males and erythrocyte cholinesterase in females. The ChE NOAEL is 0.001064 mg/L.**

This subchronic inhalation toxicity study in the rat is classified **Acceptable/nonguideline (§82-4a)**.

Dose and Endpoint: 0.001064 mg/L; NOAEL for systemic toxicity (i.e., ChE inhibition)

Comments about Study/Endpoint: Although the selected study lacks evaluation of several parameters that are normally conducted in a subchronic inhalation study, it is considered acceptable, when taken together with the previously conducted 4-week subchronic whole-body exposure inhalation toxicity studies (MRIDs 40504818 and 40645903; HED Doc. No 012544), for determination of ChE and systemic toxicity NOAELs because the most sensitive endpoint, cholinesterase inhibition of blood and brain, was evaluated. Based on the reconsideration of all of the data including the recently submitted findings, it was concluded to change the NOAEL of 0.0005 mg/L from the earlier study (MRID No.40645903) to 0.00106 mg/L from the new study (MRID No. 45134302).

3. CONCLUSIONS

In conclusion, new data have been submitted for dermal and inhalation risk assessments. The doses and endpoints selected from these and other studies are summarized in the following table. The doses and endpoints selected for the acute and chronic dietary exposure risk assessments by the HIARC on December 11, 1997 remain unchanged and are provided in the following table (for details see HED Document Nos. and 012453 and 013613).

THIS DOCUMENT PROVIDES SUPPORT FOR THE DOSES AND ENDPOINTS SELECTED FOR DERMAL AND INHALATION RISK ASSESSMENTS BY THE HIARC ON 07/19/00.

SUMMARY OF TOXICOLOGY ENDPOINT SELECTION FOR RISK ASSESSMENTS WITH ACEPHATE

EXPOSURE	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute RfD	NOAEL = 0.5	Brain cholinesterase inhibition	Acute Neurotoxicity Range Finding - Rat
	UF =100	**Acute RfD = 0.005 mg/kg**	
Chronic RfD	NOAEL = 0.12	Brain cholinesterase inhibition	90-day Feeding - Rat
	UF =100	**Chronic RfD = 0.0012 mg/kg/day**	
Short-Term Dermal	Dermal NOAEL = 50	Brain cholinesterase inhibition	21-Day Dermal - Rat
Intermediate-Term Dermal	Dermal NOAEL = 50	Brain cholinesterase inhibition	21-Day Dermal - Rat
Long-Term Dermal	Dermal NOAEL = 50	Brain cholinesterase inhibition	21-Day Dermal - Rat
Inhalation (Any duration)	Inhalation NOAEL = 0.00106 mg/L	Brain cholinesterase inhibition	4-week Inhalation - Rat

NOAEL - No Observable Adverse Effect Level , UF = Uncertainty Factor